Biomarkers: 
**Key to better rheumatoid arthritis drug development and treatment**

Iain B. McInnes, PhD, FRSE, FMedSci, Muirhead Professor of Medicine and Director of the Institute of Infection, Immunity and Inflammation, University of Glasgow, Scotland  
Mary Katherine (MK) Farmer, MD, Therapeutic Strategy Lead, Rheumatology, Senior Medical Director, Immunology and Internal Medicine Therapeutic Delivery Unit, Quintiles  
Andrew Platt, PhD, Scientific Advisor, Global Central Laboratories, Quintiles

**Executive summary**

Rheumatoid arthritis (RA) affects approximately 1% of the world’s population with an ever-increasing burden on health, quality of life and the economy.

Although scientific advances in RA have led to a better understanding of the disease and new pathways for developing treatments, there remain significant unmet needs. This white paper describes new approaches to developing more effective and sustainable therapies for RA and innovative ways to conduct RA clinical trials more efficiently, successfully demonstrating value to patients and key stakeholders. We focus on the mantra that biomarkers should be integrated into all RA clinical trials as a way to build robust data sets and validate the most useful going forward. Further, these biomarkers should span genomics, proteomics and metabolomics to reflect the fact that multiple gene polymorphisms and pathways are involved in RA pathogenesis. This requires a long-term vision but will ultimately yield definitive biomarkers that will facilitate patient stratification, inform drug development decisions and help therapies to reach the right patient at the right time in their disease progression.
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Introduction

RA is a chronic and systemic destructive inflammatory disease primarily targeting the synovial tissue around joints, and is thought to be initiated by an autoimmune response against several joint-associated self antigens. Chronically inflamed joints can lead to joint deformities and complete loss-of-function and disability. Risk factors for RA include genetic and epigenetic elements which interact with environmental factors such as smoking, gut microbiota, and likely other unknown gene-environment interactions. These ultimately lead to the breach of immunological self-tolerance and disease. Loss of self-tolerance may occur many years before symptoms of RA are seen, evidenced by the appearance of antibodies to citrullinated peptides (ACPA) up to 18 years before diagnosis.1

RA is more than a disease of the joints – it comprises a syndrome – including alterations in blood lipid profiles and increased risk of vascular comorbidity, osteoporosis, metabolic syndrome, cognitive dysfunction, depression and fatigue. Collectively, these comorbidities reduce life expectancy of RA patients by as much as five to 10 years. The consequences of the resulting devastating reduction in quality of life are personal, familial and societal. High disease activity correlates with comorbidities, and accounting for the extent to which effective therapies ameliorate these comorbidities is critical when targeting treatment outcomes.

Current management of RA is based on empirical evidence and aims to adopt the most appropriate medicines and strategies for each patient, while minimizing toxicity. In contrast, the future goal is not only to develop the next generation of therapeutics but also to stratify patients appropriately based on validated biomarkers to enhance the efficacy of existing medicines. Indeed, the use of biomarkers is increasingly being encouraged by regulators including the U.S. Food and Drug Administration (FDA).2

Current treatment approaches

Once RA is diagnosed, therapy typically begins with conventional disease-modifying anti-rheumatic drugs (cDMARDs), such as methotrexate (and/or sulfasalazine and leflunomide), sometimes in combination with glucocorticoids. If these fail as monotherapies or as a combined regimen, then the decision to progress to biologics, or bDMARDs, is usually made. Current biologics have a range of modes of action, targeting the many vulnerable nodes in the inflammatory cascade. Cytokine-targeting biologics include TNFα inhibitors, and tocilizumab, which blocks the IL-6R classic and trans signalling pathways. Cell-targeting biologics include abatacept (which inhibits T-cell activation by antigen presenting cells) and rituximab (which depletes B cells). Biologics have brought great advances at an arguably acceptable safety price, despite the fact that many are associated with serious adverse events and increased risk of infection. If biologic treatment also fails, treatment with the only small molecule inhibitor approved for RA (targeting JAK3 kinase), may be considered.3 Again, treatment decisions are mostly driven by a clinical algorithm, with empiric decision-making based on experience, particularly around safety, and cost.

The first strategic intervention – a relatively recent development – has been the decision to treat early and aggressively. Previously, treatment was delayed until aggressive intervention was merited. However, initiating therapy later in disease progression has been shown to result in faster radiographic progression, which is a good surrogate for future loss of function. Indeed, every year of delay in treatment results in an average of 1.4 units of radiographic progression.4 The target of therapy is remission, with escalating therapy until this or low disease activity is achieved. Going forward, it will be important to taper therapy to the minimum required for an optimum functional state.

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Potential new treatment approaches

The next generation of therapeutics will need to match or exceed the efficacy of existing products with regards to symptoms, signs and function – or enhance remission potential, reduce or eliminate joint damage – and support increasing adherence to target-based strategic approaches. Ideally, they will also provide benefits related to convenience (for example, with an oral formulation), strategic utility (based on dose, half-life or biomarker profile), cost and/or durability.

Many current clinical trials in rheumatological diseases are focusing on IL-17, looking particularly promising in psoriatic trials, and CD20, the molecule targeted by rituximab, approved in 2006. Interestingly, there is significant interest focused around GM-CSF and its receptor, with mavrilimumab meeting primary endpoints in a Phase II trial in patients with moderate and severe RA. However, following on from the success of tocilizumab, perhaps the most intense area of clinical development in RA is focusing on IL-6 and its receptor, with at least four compounds in ongoing trials (sarilumab, sirukumab, olokizumab and clazakizumab). In addition to these biologics, there are other small molecules at various stages of development targeting BTK, PDE4 and PI3K.

With several patents already expired or due to expire imminently, biosimilars are on the horizon for the treatment of RA. These include inter alia, biosimilars of adalimumab, etanercept and rituximab. Interestingly, there is involvement here from many biopharmaceutical companies that already have a presence in this field, plus several others that are new to the RA arena, and if nothing else, this will increase competition in the marketplace and likely drive down the cost of treatment.

Personalized approaches to RA drug development

Today, decisions on RA therapy choice are driven by factors such as clinical disease activity score; joint erosion and damage, which may or may not be quantified; functional status; co-morbidity (including vascular lipid risk, infection/chronic obstructive pulmonary disorder (COPD) or demyelination). Decisions are rarely driven by molecular or clinical classification, since RA clinicians are not at the same stage as cancer biologists, who can choose therapies based on the genetic profiles of tumors; predictive biomarkers (for example, for natural history, response or toxicity prediction); stratification; or personalization. Indeed, RA is genetically complex with more than 100 genetic risk markers now identified, with each risk allele contributing minimally to disease. Such complexity suggests a genetic signature or composite genetic prediction score may need to be generated to understand both the subtype of RA and treatment predictability.

Despite the complexity, this is an intense area of research with biomarkers being discovered, and once validated in larger clinical trials, these have the potential to help with diagnosis, prognosis and prediction of response to treatment. Such biomarkers may allow clinicians to identify the pre-disease state, when there is immune activation, the transition to arthritis, and the presence of disease activity that may respond to therapy. Thus, biomarkers can drive stratified medicine by helping answer the question of “which drug for which patient…and when…and then what?”

Indeed, research into combining clinical parameters with biomarkers of response could lead to identification of risk profiles resulting in a new step toward personalized medicine in RA. Further, the molecular understanding of the various patient subsets (for example, ACPA+ve and ACPA-ve) and the ability to personalize targeted therapies for each subset could be critical. The poll conducted during the Quintiles webinar demonstrated a majority consensus (65%) among attendees that there is value in the inclusion of biomarkers in clinical trials to facilitate personalized medicine in RA. Nevertheless, there remained a considerable proportion (31%) of attendees which only “somewhat agreed” to their usefulness and thus remain to be fully convinced. Interestingly, there was minor (4%), but still important, proportion of webinar attendees who do not believe there is value in inclusion of biomarkers for personalization purposes (Figure 1).
Potential biomarkers for use in clinical trials in RA can be categorized by intended use (diagnostic, prognostic, disease activity, predictive) or source (biological – whole blood, serum, plasma, urine, synovium, cartilage, bone; imaging – radiographs, MRI; or clinical – SJC, TJC, VAS) (Figure 2). In addition to the more widely accepted and utilized serum RF and ACPAs, biomarkers encompass evaluations of synovium and synovial fluid, bone, cartilage, as well as imaging modalities. They also include clinical biomarkers such as swollen and tender joint counts, duration of morning stiffness, HAQ scores as well as composite indices combining these modalities with laboratory measures, such as the DAS-28.

In an ideal world, diagnostic biomarkers are present with disease but lacking in the absence of disease. There are many diagnostic biomarkers in various stages of discovery, description and validation. An additional layer of complexity in defining biomarkers for RA is identifying a biomarker of use in diagnosing not only early RA, but also seronegative (RF and ACPA) RA. There are several recently identified potential diagnostic biomarkers of this type, including anti-CarP, anti-PAD4, anti-BRAF, anti-RA 33, anti-Sa, and 14 novel autoantigens identified by phase display. These may have the potential to serve as markers of early disease, and to support a diagnosis of RA or undifferentiated inflammatory arthritis in those seronegative for RF and ACPA.

Prognostic biomarkers measure the progression of disease or are associated with disease outcome. In RA, the presence/magnitude of ACPA/RF, the shared epitope HLA-SE, presence of erosive disease at baseline, and a high CRP at presentation all serve as prognostic biomarkers. Thus, a prognostic picture can be painted with a combinatorial biomarker approach. Some diagnostic biomarkers also have the potential to be used prognostically, including anti-CarP. Disease activity monitoring biomarkers continue to be investigated, and the VectraDA® multi-biomarker disease activity (MBDA) test from Crescendo Bioscience (now a Myriad Company) is available and covered by Medicare in the U.S. Biomarkers in development that reflect cartilage degradation and subchondral bone erosion and turnover will help in tracking disease activity and include MMPs, urine CTX-II, serum CTX-I, ITCP, as well as osteoprotegerin (OPG), YKL-40 (human cartilage glycoprotein 39), RANKL, osteocalcin and P1NP.

Predictive biomarkers used to forecast or measure the response to therapy, however, are still in their infancy in the RA space. With up to 40% of patients having active disease despite biologic therapy, the hope is that determination of biomarkers to predict which patients are likely to respond to a given therapy will allow targeted selection of the best biologic for each patient, exemplifying the concept of personalized medicine. There are several compelling pharmacogenomic data sets assessing baseline proteomic
signatures and SNPs, which can predict response to methotrexate and TNFα inhibitors. There is much to gain from additional research in this area and we wait with great anticipation to see if such signatures hold true in larger clinical trials.

Due to the highly complex nature of RA, it will be critical to harness the combined power of genomics, epigenetics, proteomics and metabolomics to direct decision-making in RA treatment going forward (Figure 2). Further, clinically useful biomarkers will be informed by an improved understanding of pathogenesis, and looking for effects of therapies in all comorbidities, not exclusively the impact on the inflamed joints. However, while the potential for efficacy of a combinatorial biomarker strategy is encouraging, it is not yet clear whether this approach will prove economically feasible.

**Synovial fluid and synovial membrane interrogation**

In stark contrast to the normal synovium, which has a paucity of inflammatory cells, the rheumatoid synovium is home to inflammatory leukocytes including macrophages, neutrophils, mast cells, and T and B lymphocytes. It is also marked by neoangiogenesis and lymphangiogenesis, which together facilitate immune cell mobilization to the inflamed synovium.

There are several methods of obtaining synovium by biopsy. Arthroscopy-guided synovial biopsy allows direct visualization of the rheumatoid pannus for sampling. In the past few years, however, power doppler ultrasound (PDUS) has increasingly gained popularity as a non-invasive measure, detecting active synovitis and allowing an appropriate site for biopsy to be selected. These are conducted in a minimally invasive fashion using 4mm 11-14 gauge soft tissue biopsy needles to obtain samples according to the target joint. The knee has historically been the most common target, although with ultrasound there are other possibilities, including the wrist, ankle and MCP joint. These ultrasound-guided biopsies can be conducted by a rheumatologist with specialized training, whereas arthroscopy is reserved for those with surgical training.

Synovial biopsy has the potential to become a rapidly evolving tool in early phases of clinical research in RA, and is being used increasingly in both first-in-human/phase 1 as well as phase 2 studies. It is unlikely to be broadly utilized in a phase 3 clinical trial, but rather utilized in the setting of a substudy, as this procedure is not part of routine standard of care, and requires additional training and equipment to perform.
**Imaging biomarkers**

Measurement of radiographic disease progression has been an integral part of RA drug development and has historically been measured by conventional radiography. Rates of radiographic progression on x-ray within the timeframe of a clinical trial have not been observed. A recent article by Landewé et al suggests a different approach, employing the maintenance of structural integrity rather than inhibition of radiographic progression as an endpoint.7

While x-rays are considered as the gold standard to evaluate structural damage, limitations include low sensitivity and an inability to assess disease activity. In an attempt to overcome these limitations, several other imaging modalities have been used to varying degrees. MRI directly visualizes synovitis, bone marrow edema and erosions and quantitative output using RAMRIS scoring. MRI evaluation is increasingly undertaken in the clinic and utilized in many clinical trials. Despite the advantages of OMERACT RAMRIS scores for quantitation of MRI in RA (including that they are suitable for multicenter trials), relatively few clinical trials have adopted them; this is perhaps due to the relatively poor sensitivity to synovial change, which is one of the areas of greatest interest in the earlier stages of drug development. Additional methods for MRI assessment in RA are highly likely to be developed in the future.

**Conclusion**

Looking ahead, a combined panel of biomarkers is required to identify early disease or even pre-disease, and in those who are seronegative – combined with additional diagnostic, prognostic and predictive biomarkers – to identify those likely to have an aggressive and/or destructive course and respond to specific treatment regimens. This would enable treatment to be tailored to maintain structural integrity and preserve function and quality of life. Ongoing collaborative efforts such as those led by OMERACT will continue to help drive progress. A recent article by Kim and Paget noted that “the ultimate utility of biomarkers as a composite of clinical, molecular and imaging assessments is to enable early diagnosis, stratification, and tracking of disease activity, and selection of, and response to treatment.”8 This potential can be achieved by incorporating biomarkers throughout drug development. Indeed, robust and validated biomarkers have great potential to help accelerate development of therapies and prevent irreversible damage to help patients lead more enjoyable and productive lives.
References


About the authors

Professor Iain B. McInnes
Muirhead Professor of Medicine and Director of the Institute of Infection, Immunity and Inflammation, University of Glasgow

Prof. Iain B McInnes leads a trials unit specialising in use of biologic agents in inflammatory arthritis early clinical trials, and is published widely in areas of immunobiology and rheumatology. He is Associate Editor, *Annals of Rheumatic Diseases*, member, Editorial Board of *European Journal of Immunology*. Research interests include understanding the role of cytokines in inflammatory synovitis. Iain is a recipient of the Michael Mason Prize from the British Society for Rheumatology, and holds multiple lectureships from organizations in the U.K., Canada, Germany, Sweden and the U.S. He is a previous Chairman of the EULAR Scientific Committee, current Liaison Officer ACR for the European League Against Rheumatism, and an Elected Fellow, Royal Society of Edinburgh, Academy of Medical Sciences. Iain studied medicine at the University of Glasgow, where he trained in internal medicine and rheumatology. He has completed his membership of the Royal College of Physicians, and is also a Fellow. He completed a Ph.D. and post-doctoral studies via fellowships from the Wellcome Trust, Arthritis Research Campaign, and the U.S. National Institutes of Health Fogarty Fellowship Programme.

Mary Katherine Farmer, MD
Senior Medical Director & Rheumatology Strategy Lead, Quintiles

Dr. Mary Katherine (MK) Farmer advises customers on studies and programs in rheumatologic disease and related conditions. She provides therapeutic strategy, due diligence and business planning for potential partnerships with sponsors. Areas of interest include patient-reported outcomes, biomarkers in RA and lupus, disease scales and quality of life as well as maintenance of function. MK has extensive experience conducting clinical trials and as a treating physician. She has published on a variety of topics and authored the lupus chapter of a popular internal medicine textbook. Her research on lupus nephritis was presented at the American College of Rheumatology. MK received her M.D. from Medical College of Georgia, and completed her internship and residency in internal medicine at Richland Memorial Hospital and Dorn VA Medical Center, Columbia, South Carolina. She completed a Rheumatology fellowship at University of North Carolina, Chapel Hill, and is Board certified in both Internal Medicine and Rheumatology.
Andrew Platt, PhD
Scientific Advisor, Scientific Review Team, Global Central Laboratories, Quintiles
Andrew (Andy) Platt, Ph.D., is an immunologist and provides therapeutic and protocol-specific insight to biomarker strategy decisions in clinical trial design for studies relating to autoimmunity and inflammation. Prior to joining Quintiles, Andy spent many years in academia in the U.K. and U.S., and with a particular focus on inflammatory bowel disease and rheumatoid arthritis (RA), researched key immunological mechanisms driving inflammation and immune cell mobilization. In addition to several book chapters and reviews, he has published numerous primary articles around understanding basic immune mechanisms in addition to the mode of action of biologics and small molecule kinase inhibitors approved or in development for the treatment of RA. Andy completed both his B.Sc (Hons) degree and Ph.D. in Immunology at the University of Glasgow, U.K. Here, Andy was the recipient of the British Society for Immunology Undergraduate Prize, and the Joseph Black Medal and Alan Hird Prize in Medicine for his doctoral thesis.